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The use of cyclosporine for Stevens-Johnson syndrome-toxic epidermal necrolysis spectrum at the University of Louisville: A case series and literature review

Clayton D Conner MSc, Emily McKenzie MD, Cindy E Owen MD, Jeffrey P Callen MD

Affiliations: Division of Dermatology, University of Louisville School of Medicine, Louisville, Kentucky

Corresponding Author: Cindy E. Owen MD, Division of Dermatology, University of Louisville School of Medicine, 3810 Springhurst Boulevard, Suite 200, Louisville, KY 40241, Tel: ceowen01@louisville.edu

Abstract

Introduction: Cyclosporine therapy for Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) was first reported in the literature by Renfro et al. in 1989. Herein we report an additional 4 cases of SJS-TEN treated with cyclosporine.

Methods: Case information was collected retroactively at the University of Louisville Hospital in Louisville, KY. All cases had a diagnosis of SJS or TEN by a dermatologist. All patients were ≥18 years of age and treated with cyclosporine during their admission.

Results: Three of four patients re-epithelialized within an average of 3.67 days of starting 3-4 mg/kg/day of cyclosporine. One patient passed away, likely due to advanced endometrial cancer.

Discussion: We provide a review of the literature on cyclosporine use for SJS/TEN, including various outcome measures — stabilization (cessation of new lesions), time to re-epithelialization, mortality rate, and hospital length of stay and, where available, comparison to other systemic agents.

Conclusion: The outcomes appear to be consistent with rapid re-epithelialization and low mortality as seen in many previous reports. Treating SJS-TEN with systemic agents including cyclosporine will remain controversial because the vast majority of data comes from case reports, case series, or small open prospective trials.

Keywords: Stevens-Johnson syndrome, SJS, toxic epidermal necrolysis, TEN, cyclosporine, re-epithelialization, SCORTEN

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of disease and are considered severe cutaneous adverse reactions (SCARs). SJS/TEN eruptions begin as purpuric macules evolving over the course of hours to days into tender, flaccid blisters first appearing on the trunk then spreading to the neck, face, upper arms, palms, and soles. Buccal, ocular, and genital mucosae are involved in 90% of patients. Respiratory and gastrointestinal mucosa involvement is less common. The distinction between SJS and TEN is based on the amount of body surface area involved. Grade 1 (SJS) is defined as <10% mucosal erosion and epidermal detachment. Grade 2 (Overlap SJS/TEN) exhibits 10-30% epidermal detachment. Grade 3 (TEN) demonstrates >30% epidermal detachment. SJS and TEN are most commonly caused by medications (50% and 95%, respectively). Among the highest risk medications are nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, co-trimoxazole, other anti-infective sulfonamides, sulfasalazine, allopurinol, and oxicam NSAIDs [1]. Due to the rarity of SJS and TEN (annual incidence of 1.2-6.0 and 0.4-1.2 per million persons, respectively), there are few randomized controlled trials evaluating treatment [2]. Mortality risk can be predicted using the SCORTEN scoring system, first described by Bastuji-Garin et al. as seven binary parameters calculated on days 1 and 3 of admission [3]. It has been shown by Cartotto et al. to be a good

prognostic tool in patients throughout the SJS-TEN spectrum, especially in those being treated in a burn center [4].

After discontinuing the potentially inciting agent, management typically consists of supportive care in an intensive care or burn unit, as fluid and electrolyte loss can be a significant concern. The use of systemic agents is debatable as there is only retrospective data regarding their efficacy, with the exception of one randomized control trial demonstrating the ineffectiveness of thalidomide in SJS/TEN [21]. Cyclosporine has been proposed as a treatment based on the recognition of granulysin as a key player in the apoptosis observed in TEN [9, 10]. As a calcineurin inhibitor, cyclosporine impairs interleukin-2 (IL-2), tumor necrosis factor (TNF), IL-3, IL-4, CD40L, interferon-gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF) transcription, thus reducing T cell proliferation, which could explain its salutary effect. As with any medical intervention in SJS-TEN, the therapeutic window is narrow. Renal insufficiency remains the most common reason for premature discontinuation, as acute renal failure occurs in up to 20% of all SJS-TEN cases. It is our aim that this series of four cases and review of the current literature will shed additional light on better treating this devastating disease.

Methods

Case information was collected retroactively at the University of Louisville Hospital (ULH) in Louisville, KY. All cases had a clinical or histopathological diagnosis of SJS or TEN by a dermatologist. All patients were ≥18 years of age and treated with cyclosporine during their admission. Due to the limited size of this case series, the project was considered institutional review board (IRB) exempt.

Results

Case #1

The patient was a 23-year-old Caucasian woman being treated for schizophrenia at a psychiatric hospital. After starting carbamazepine 20 days prior, she developed erythematous papules, vesicles, and bullae on her face, conjunctival injection, and oral erosions. Her conditioned worsened over the next 7 days, upon which she presented to ULH and received a diagnosis of SJS with a SCORTEN of 1. She was promptly started on 3 mg/kg/day of cyclosporine divided twice daily for three days with re-epithelialization occurring on day 4 of therapy. While hospitalized, she experienced no adverse events, and the SJS eventually resolved.

Case #2

The patient was a 77-year-old African-American woman with a past medical history of asthma, stroke, hyperlipidemia, hypertension, hypothyroidism, prediabetes, and shingles, and a recent diagnosis of endometrial cancer. Approximately 6 hours after receiving IV contrast for a staging CT scan at an outside hospital, she developed flesh colored papules on her face and arms with surrounding hyperpigmentation. Over the next 24 hours, swelling developed in her hands, face, lips, and tongue, and the papules on her face and arms evolved into painful bullae. She was admitted to the hospital and started on IV prednisone, which she received until being transferred to ULH on hospital day 10. Upon examination, she received a diagnosis of TEN with a SCORTEN of 5. She was quickly started on 3 mg/kg/day of cyclosporine divided twice daily, but only for one day. Due to her worsening condition, the decision was made to transition to comfort care only. Lifesaving care was subsequently withdrawn, and she expired.

Case #3

The patient was a 62-year-old Caucasian male with a past medical history of atrial fibrillation, congestive heart failure, hypertension, and chronic kidney disease secondary to glomerulonephritis. After taking trimethoprim-sulfamethoxazole for 98 days, he developed erythematous macules and patches with desquamation on his arms, abdomen, and groin, as well as erosions with hemorrhagic crusting on his face and oral mucosa. These mucocutaneous findings worsened during the 10 days leading up to his presentation to an outside hospital, where he spent 5 days before being transferred to ULH. He received a diagnosis of TEN, a SCORTEN of 4, and began taking 3 mg/kg/day of cyclosporine divided twice daily for four days. He re-epithelialized on day 3 of therapy, experienced no adverse events, and the TEN eventually resolved.

Case #4

The patient was a 31-year-old African-American male with no significant past medical history taking trimethoprim-sulfamethoxazole. On day 5 of therapy, he developed tender erythematous plaques on his back, erosions in his groin, perioral crusting, and conjunctival injection. He presented to ULH 4 days later and received a diagnosis of SJS with a SCORTEN of 1. He was started on 3 mg/kg/day of cyclosporine divided twice daily for five days with re-epithelialization occurring on day 4. During the hospital course, the patient experienced no adverse events, and the SJS eventually resolved.

Discussion

To the best of our knowledge, cyclosporine therapy for SJS-TEN has been reported in 12 previous publications involving 183 patients, beginning with Renfro et al. in 1989 [11]. Authors have included a variety of outcome measures, namely stabilization (cessation of new lesions), time to re-epithelialization, mortality rate, and hospital length of stay. For a more succinct review of the reports, please refer to **Table 3**. In Renfro's unprecedented report, a patient stabilized and re-epithelialized within 3 days of starting cyclosporine and had a hospital stay of 10 days [11]. Seven years later in 1996, Sullivan et al. published a patient that stabilized within 24 hours of starting cyclosporine, achieved complete re-epithelialization in 2 weeks, and had a hospital stay of 72 days [12]. In another case report by Jarrett et al., a patient stabilized within hours of starting cyclosporine and achieved complete re-epithelialization within 12 days [13]. In 2000, Arévalo et al. published the first case series comparing cyclosporine (n=11) to cyclophosphamide and corticosteroids (n=6). Their group reported an average re-epithelialization time of 12.0 days with cyclosporine compared to 17.6 days with cyclophosphamide and corticosteroids. A more favorable mortality rate with cyclosporine was also of note, which was 0 of 11 compared to 3 of 6 [7]. Hashim et al. describes a patient that stabilized within 24 hours of beginning therapy and completely re-epithelialized within 72 hours [14]. A similar report by Aihara et al. recounts a patient with TEN that stabilized within 24 hours of starting cyclosporine, had completely re-epithelialized in 14 days, and had a hospital stay of 43 days [15]. In 2010, Valeyrie-Allanore et al. published the first open phase II trial consisting of 29 patients. By day 3 of therapy, 62% of patients had stabilized with cyclosporine compared to 35% with IVIG. Despite SCORTEN predicting 2.75 deaths, there were no mortalities. The average re-epithelialization time was 12.57 days [16]. Three of the 29 patients experienced side effects that prompted discontinuing therapy, including acute hallucinations from suspected reversible posterior leukoencephalopathy, transient neutropenia, and nosocomial pneumopathy. Two patients were tapered earlier than scheduled due to mild renal insufficiency. In a 2011 case series of 4 patients, Reese et al. reported no further progression after starting cyclosporine and a mortality rate of 0 of 4 patients [17]. Later that year, Carmona et al. published a case series of 3 patients that stabilized within 48 hours of starting therapy, re-epithelialized within 11.67 days on average, and experienced no mortalities [18]. In an open uncontrolled study of 17 patients, Singh et al. compared retrospective data of those treated with cyclosporine versus corticosteroids. Patients treated with cyclosporine stabilized in 3.18 days on average and 4.75 days with corticosteroids. Complete re-epithelialization occurred in 14.54 days with cyclosporine and 23.0 days with corticosteroids. The mortality rate was 0 of 11 with cyclosporine and 2 of 6 with corticosteroids. Hospital stay was 18.09 days with cyclosporine and 26 days with corticosteroids [19]. In 2014, Kirchhof et al. published a retrospective review of 64 patients treated conservatively (n=12), with IVIg (n=35), with cyclosporine (n=15), and with both IVIg and cyclosporine (n=2). Mortality rates were 1 of 13 with cyclosporine (despite 2.4 predicted with SCORTEN) compared to 11 of 37 with IVIg (only 7.4 predicted with SCORTEN). This translated to a more favorable standardized mortality ratio (SMR = sum of observed deaths/sum of expected deaths) of 0.42 with cyclosporine versus 1.43 with IVIg [8]. Most recently, Lee et al. published a retrospective cohort of 44 patients treated with either cyclosporine (n=24) or supportive care only (n=20). Treatment with cyclosporine showed a mortality rate of 3 of 24 despite 7.18 predicted with SCORTEN, which compared to 6 of 20 with supportive care only (5.90 predicted). This rendered an auspicious SMR of 0.42 with cyclosporine versus 1.02 with supportive care only. Adjusting for SCORTEN, Charlson comorbidity index, and days of delay to admission, risk ratio for death with cyclosporine versus supportive care was

Table 1. *SCORTEN scoring system for predicting patient outcome in TEN [3]*

SCORTEN Parameters	Points
>10% epidermal detachment	0 or 1
Age >40 years	0 or 1
History of malignancy	0 or 1
Heart rate >120 BPM	0 or 1
Urea >10 mmol/L	0 or 1
Glucose >14 mmol/L	0 or 1
Bicarbonate <20 mmol/L	0 or 1
Total	0 - 7

SCORTEN Total Points	Predicted Mortality Rate (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
≥5	90.0

Table 2. *Patient demographics and clinical features*

	Case #1	Case #2	Case #3	Case #4
Sex	Female	Female	Male	Male
Age	23 years	77 years	62 years	31 years
Race/ethnicity	White	Black	White	Black
Comorbidities		Endometrial cancer		
Diagnosis	SJS	TEN	TEN	SJS
Etiology	Carbamazepine	IV contrast	TMP/SMX	TMP/SMX
Description of lesions	Erythematous papules, vesicles, and bullae on face; conjunctival injection; oral erosions	Bullae on face and arms	Erythematous macules and patches with desquamation on arms, abdomen, and groin; erosions with hemorrhagic crusting on face and oral mucosa	Tender erythematous plaques on back; erosions in groin; perioral crusting; conjunctival injection
SCORTEN	1	5	4	1
Day at presentation	2	10	5	3
Dose of cyclosporine	3 mg/kg/day (given in divided doses BID)	3 mg/kg/day (given in divided doses BID)	3 mg/kg/day (given in divided doses BID)	3 mg/kg/day (given in divided doses BID)
Length of treatment	3 days	1 day	4 days	5 days

	Case #1	Case #2	Case #3	Case #4
Time to re-epithelialization	4 days	N/A	3 days	4 days
Adverse events	None	Care Withdrawn	None	None
Outcome	Resolved	Deceased	Resolved	Resolved
Miscellaneous information		10 days of IV prednisone prior to arrival	Transfer from outside facility	

Table 3. *Chronologic summary of cyclosporine usage in SJS-TEN spectrum.*

Authors	Year	# of Patients	Dx	Etiology	Treatment(s)	Outcome(s)	Complication(s)
Renfro et al. [11] [PMID: 2777442]	1989	1	TEN	Phenytoin	Cyclosporine	Stabilized and re-epithelialized within 3 days. Hospital stay of 10 days.	None
Sullivan et al. [12] [PMID: 8961591]	1996	1	TEN	Lamotrigine	1. IV hydrocortisone 300mg 2. dexamethasone 4mg QID x 3 days 3. IV cyclosporine 4.5 mg/kg/day x 16 days	Stabilized within 24 hours. Complete re-epithelialization in 2 weeks. Hospital stay of 72 days.	None
Jarrett et al. [13] [PMID: 9536553]	1997	1	TEN	Carbamazapine	IV cyclosporine 5mg/kg	Stabilized within hours. Complete re-epithelialization within 12 days.	None
Arévalo et al. [7] [PMID: 10744287]	2000	17	TEN	Allopurinol (2), NSAID (2), Metamizol (1), Ranitidine (1), Corticosteroids (3). Tetrabamate (1), Septrim (1), Phenytoin (1), Carbamazepine (1), Aspirin (1), Paracetamol (1), Vitamin B (1)	Oral cyclosporine 3mg/kg/day divided twice daily (11) vs. cyclophosphamide 150 mg Q12H and corticosteroids (6)	Complete re-epithelialization within 12.0 days vs. 17.6 days with cyclophosphamide and corticosteroids. Mortality rate 0 of 11 vs. 3 of 6 with cyclophosphamide and corticosteroids.	None
Hashim et al. [14] [PMID: 15040495]	2003	1	Overlap SJS/TEN	Lamotrigine	Cyclosporine 2 mg/kg/day divided twice daily x 4 days	Stabilized within 24 hours. Completely re-epithelialized within 72 hours.	

Authors	Year	# of Patients	Dx	Etiology	Treatment(s)	Outcome(s)	Complication(s)
Aihara et al. [15] [PMID: 17875095]	2007	1	TEN	Unknown	1. Oral prednisolone 40mg daily 2. IV ulinatatin 3. IV cyclosporine 1 mg/kg/day with methylprednisolone (30 mg/kg/day) x 3 days	Stabilized within 24 hours. Completely re-epithelialized within 14 days. Hospital stay of 43 days.	
Valeyrie-Allanore et al. [16] [PMID: 20500799]	2010	29	SJS (10) SJS/TEN (12) TEN (7)	Nevirapine (4), Lamotrigine (3), Sulfonamides (3), Amifostine (3), Carbamazepine (2), Quinolones (2), Allopurinol (1), Oxicam (1)	Oral Cyclosporine 3 mg/kg x 10 days	62% of patients stabilized at day 3 vs. 35% with IVIG. Mortality rate 0 of 29 (2.75 predicted with SCORTEN). Re-epithelialization within 12.57 days	Acute hallucinations (suspected reversible posterior leukoencephalopathy) (n=1), Transient neutropenia (n=1), Severe infection (nosocomial pneumopathy) (n=1), mild renal insufficiency (n=2)
Reese et al. [17] [PMID: 21323097]	2011	4	SJS/TEN	TMP-SMX (2) Lamotrigine (1) Acetaminophen (1)	Cyclosporine 5 mg/kg/day divided twice daily	No further progression in any patients. No deaths.	
Carmona et al. [18] [PMID: 21215491]	2011	3	TEN	Allopurinol (2) Amoxicillin-clavulanic acid (1)	Cyclosporine 3 mg/kg/day divided twice daily	Stabilized within 48 hours. Re-epithelialized within 11.67 days. Mortality rate 0 of 3.	
Singh et al. [19] [PMID: 23974585]	2013	17	SJS (8), Overlap SJS/TEN (4), TEN (5)	Ofloxacin (1), Dilantin (2), Norfloxacin (1), Ciprofloxacin (1), Ibuprofen (3), Tinidazole (1), Dilantin (1), Carbamazepine (1), Unknown (1)	Cyclosporine 3 mg/kg/day divided three times daily (open, uncontrolled trial) vs. corticosteroids (retrospective data)	Stabilized within 3.18 days vs. 4.75 days with corticosteroids. Complete re-epithelialization within 14.54 days vs. 23.0 days with corticosteroids. Mortality rate 0 of 11 vs. 2 of 6 with corticosteroids. Hospital stay 18.09 days vs. 26 days with corticosteroids.	

Authors	Year	# of Patients	Dx	Etiology	Treatment(s)	Outcome(s)	Complication(s)
Kirchhof et al. [8] [PMID: 25087214]	2014	64	SJS (28), Overlap SJS/TEN (19), TEN (17)	Not reported	12 patients treated conservatively 35 patients: IVIg (average 1mg/kg/day x 3 days) 15 patients: Cyclosporine (average 3-5 mg/kg/d x 7 days) 2 patients: both IVIg and Cyclosporine	Mortality rate 1 of 13 (2.4 predicted with SCORTEN) vs. 11 of 37 with IVIg (7.4 predicted with SCORTEN). SMR 0.42 vs. 1.43 with IVIg.	
Lee et al. [20] [PMID: 27717620]	2017	44	SJS (16) Overlap SJS/TEN (12), TEN (16)	Not reported	24 patients treated with cyclosporine, Creteil: 3 mg/kg/d for 10 days, followed by 2 mg/kg/d for 10 days, and lastly 1 mg/kg/d for 10 days; administered orally or via nasogastric tubes; any prior immunomodulating agents were stopped 20 patients treated supportively	Mortality rate 3 of 24 (7.18 predicted with SCORTEN) vs. 6 of 20 with supportive care only (5.90 predicted with SCORTEN). SMR of 0.42 vs. 1.02 with supportive care only. Risk ratio for death with cyclosporine vs. supportive care was 0.49. Length of hospital stay 20 days vs. 14 days with supportive care only.	

0.49. Interestingly, the average length of hospital stay was 20 days with cyclosporine versus 14 days with supportive care only [20]. The patients in our case series performed similarly in the context of other accounts of cyclosporine use in SJS-TEN spectrum. In our four patients, re-epithelialization occurred within an average of 3.67 days and the only mortality was likely secondary to advanced endometrial cancer.

Conclusion

In this case series, we report 4 patients, 3 of whom experienced rapid re-epithelialization on cyclosporine and one who died from complications of advanced malignancy one day after starting cyclosporine. The results in our series appear to be consistent with many previous observations on this topic. A review of the current literature produces evidence of rapid stabilization, rapid re-epithelialization, low mortality rate, and shortened hospital length of stay with cyclosporine therapy. Although there are no randomized controlled trials comparing cyclosporine to other system therapies or supportive care only, cyclosporine appears to be safe and effective for the treatment of SJS-TEN. Despite the growing number of reports, treating SJS-TEN patients with cyclosporine will likely remain controversial because the vast majority of the data has come from the case reports, case series, or small open prospective trials we have reviewed in this article. The limitations of this case series are similar to previous studies on this topic. This is a retrospective study at a single center, which is not optimal when compared to multi-center, double-blinded, controlled trials. Unfortunately, these limitations are unlikely to be overcome in the near future due to the rarity of SJS-TEN. Perhaps future collaboration and standardization of outcome measures between centers will lead to more impactful data analysis and insight.

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